OIPE IAP96
SEP 29 2006
PATENT & TRADEMARK OFFICE

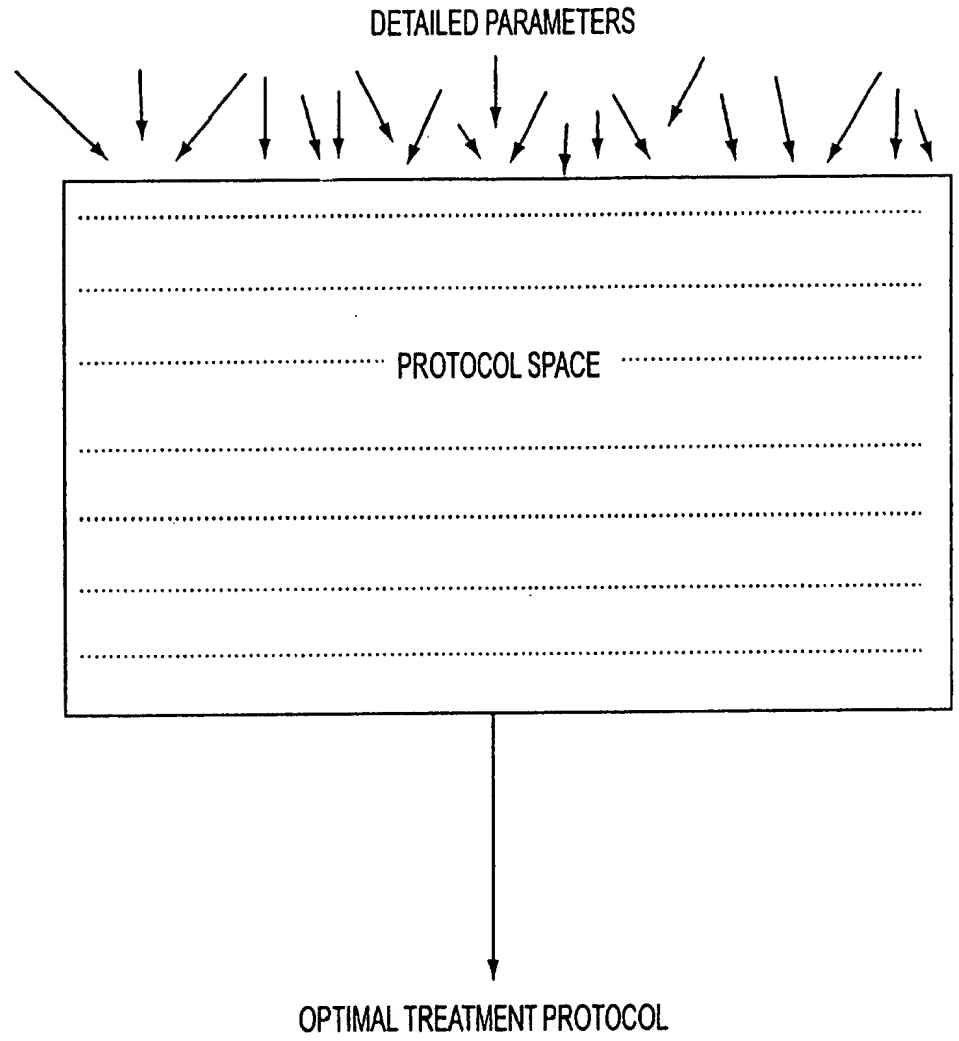

FIG. 1

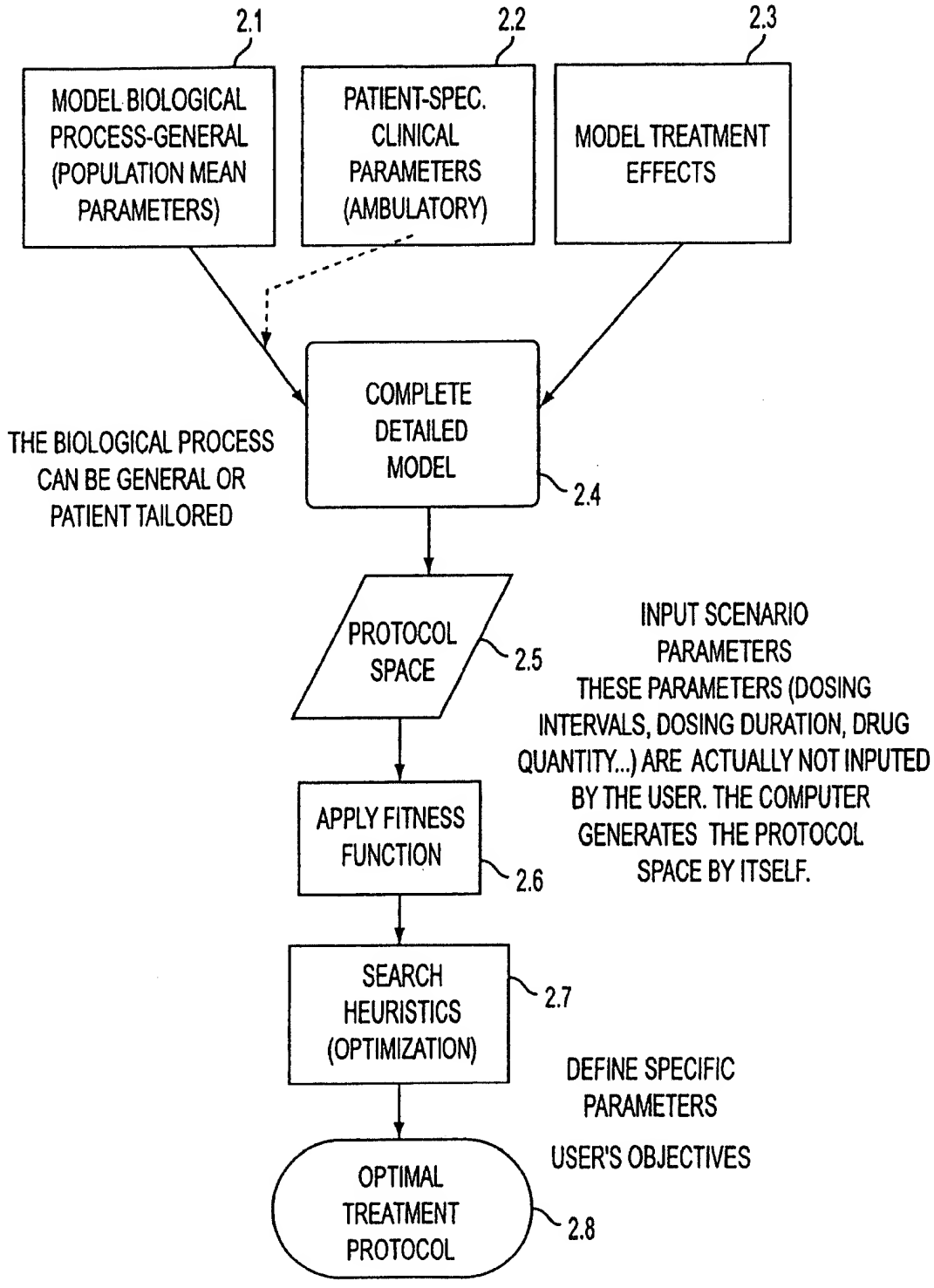
2.1
2.2
2.3
MODEL BIOLOGICAL PROCESS-GENERAL (POPULATION MEAN PARAMETERS)
PATIENT-SPEC. CLINICAL PARAMETERS (AMBULATORY)
MODEL TREATMENT EFFECTS
COMPLETE DETAILED MODEL
2.4
THE BIOLOGICAL PROCESS CAN BE GENERAL OR PATIENT TAILORED
PROTOCOL SPACE
2.5
INPUT SCENARIO PARAMETERS
THESE PARAMETERS (DOSING INTERVALS, DOSING DURATION, DRUG QUANTITY...) ARE ACTUALLY NOT INPUTED BY THE USER. THE COMPUTER GENERATES THE PROTOCOL SPACE BY ITSELF.
APPLY FITNESS FUNCTION
2.6
SEARCH HEURISTICS (OPTIMIZATION)
2.7
DEFINE SPECIFIC PARAMETERS
USER'S OBJECTIVES
OPTIMAL TREATMENT PROTOCOL
2.8

FIG. 2A

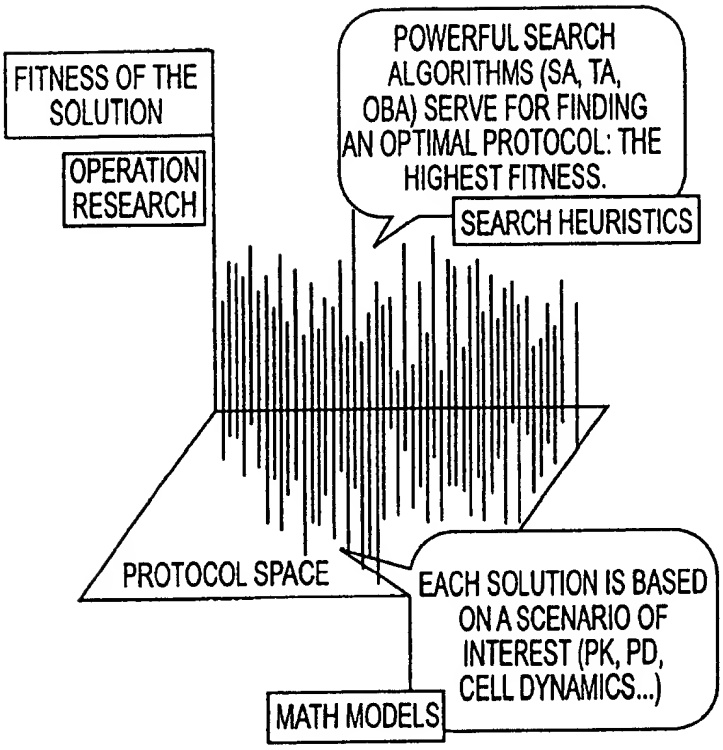
FITNESS OF THE SOLUTION
OPERATION RESEARCH
POWERFUL SEARCH ALGORITHMS (SA, TA, OBA) SERVE FOR FINDING AN OPTIMAL PROTOCOL: THE HIGHEST FITNESS.
SEARCH HEURISTICS
PROTOCOL SPACE
EACH SOLUTION IS BASED ON A SCENARIO OF INTEREST (PK, PD, CELL DYNAMICS...)
MATH MODELS

FIG. 2B

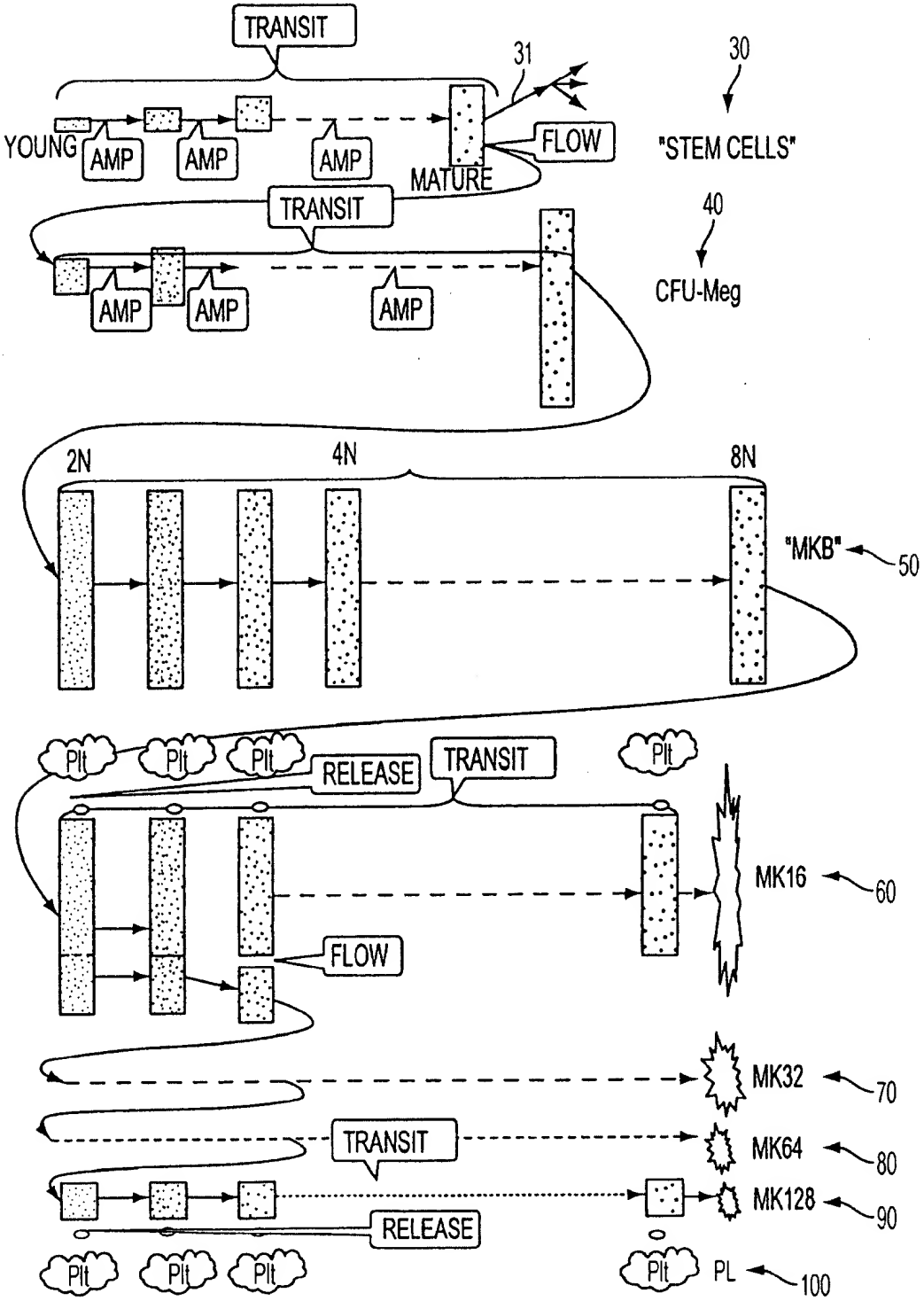
TRANSIT
31
30
YOUNG
AMP
AMP
AMP
MATURE
FLOW
"STEM CELLS"
TRANSIT
40
CFU-Meg
AMP
AMP
AMP
2N
4N
8N
"MKB"
50
Plt
Plt
Plt
RELEASE
TRANSIT
Plt
MK16
60
FLOW
MK32
70
TRANSIT
MK64
80
MK128
90
RELEASE
Plt
Plt
Plt
Plt
PL
100

FIG. 3

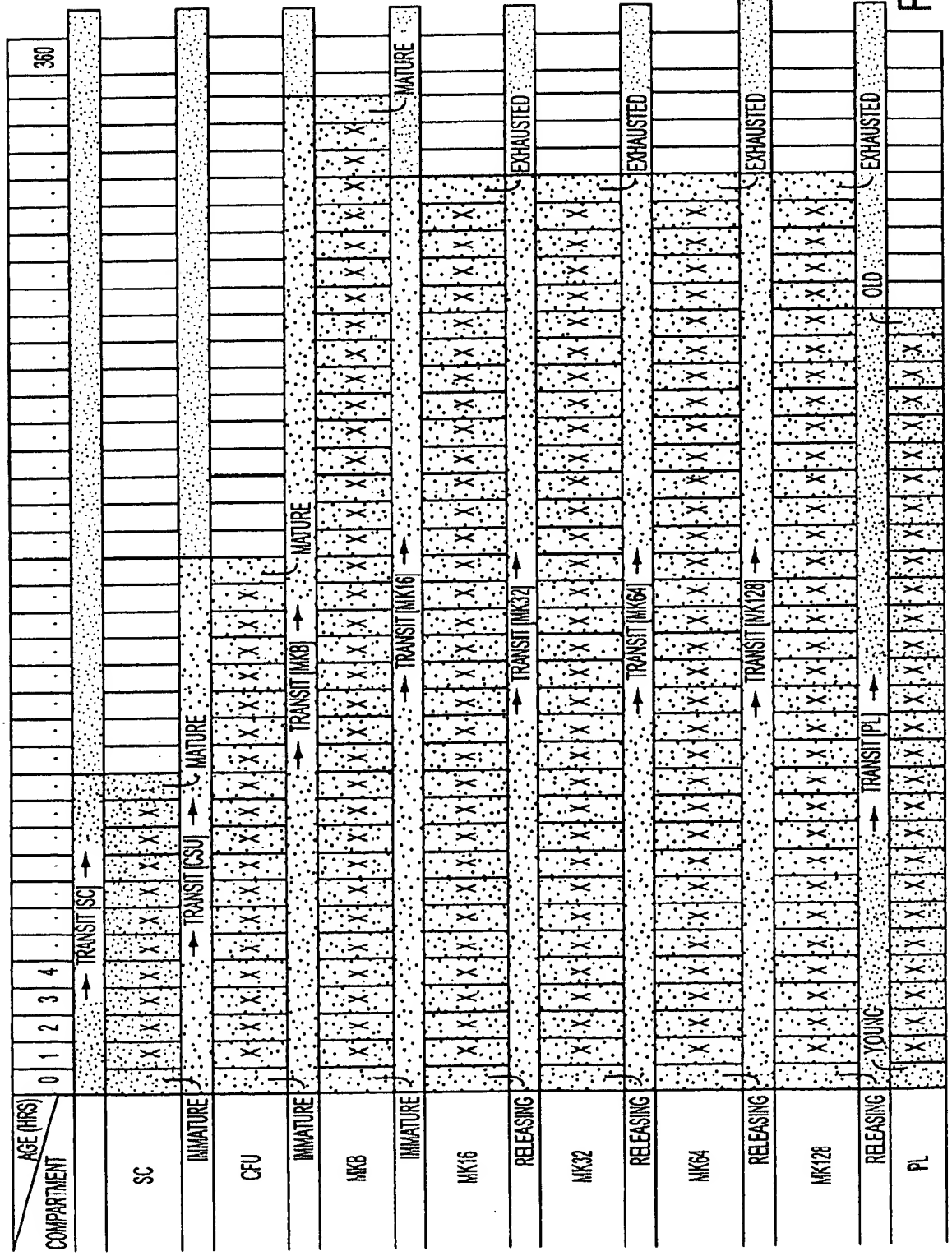
AGE (HRS)
COMPARTMENT
0
1
2
3
4
360
SC
IMMATURE
CFU
IMMATURE
MKB
IMMATURE
MK16
RELEASING
MK32
RELEASING
MK64
RELEASING
MK128
RELEASING
PL
TRANSIT [SC]
TRANSIT [CSU]
MATURE
TRANSIT [MKB]
MATURE
TRANSIT [MK16]
MATURE
TRANSIT [MK32]
EXHAUSTED
TRANSIT [MK64]
EXHAUSTED
TRANSIT [MK128]
EXHAUSTED
TRANSIT [PL]
YOUNG
OLD
EXHAUSTED

FIG. 4

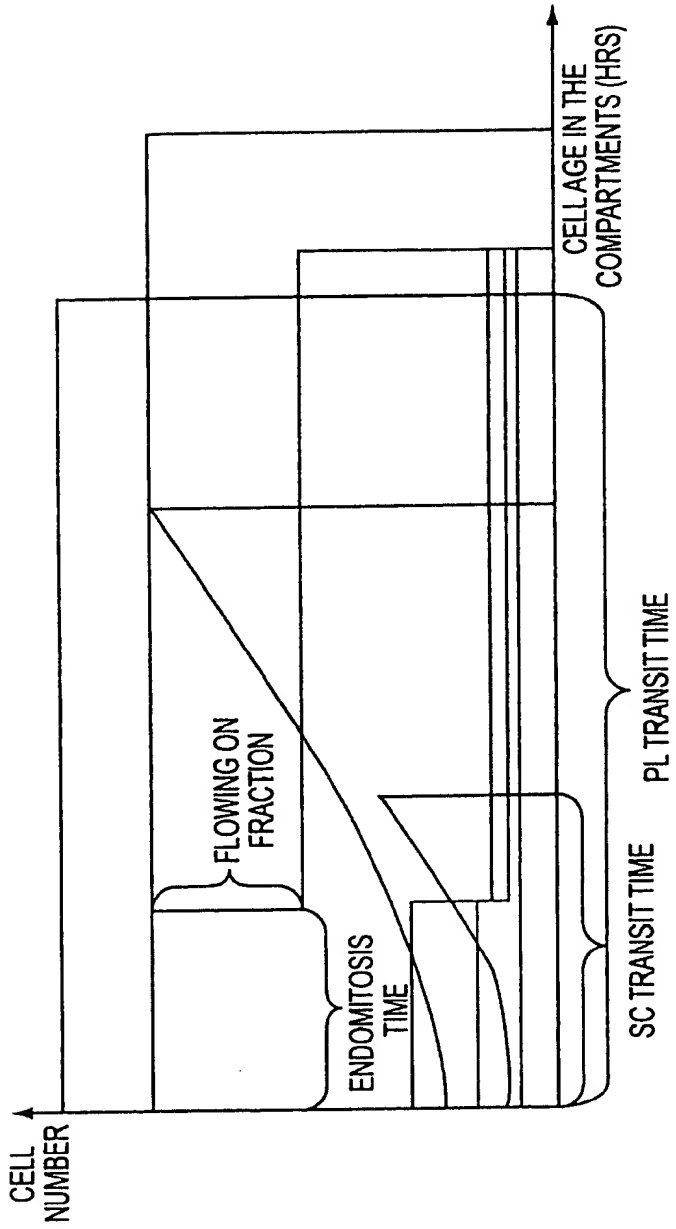
CELL AGE IN THE COMPARTMENTS (HRS)
CELL NUMBER
FLOWING ON FRACTION
ENDOMITOSIS TIME
SC TRANSIT TIME
PL TRANSIT TIME

FIG. 5

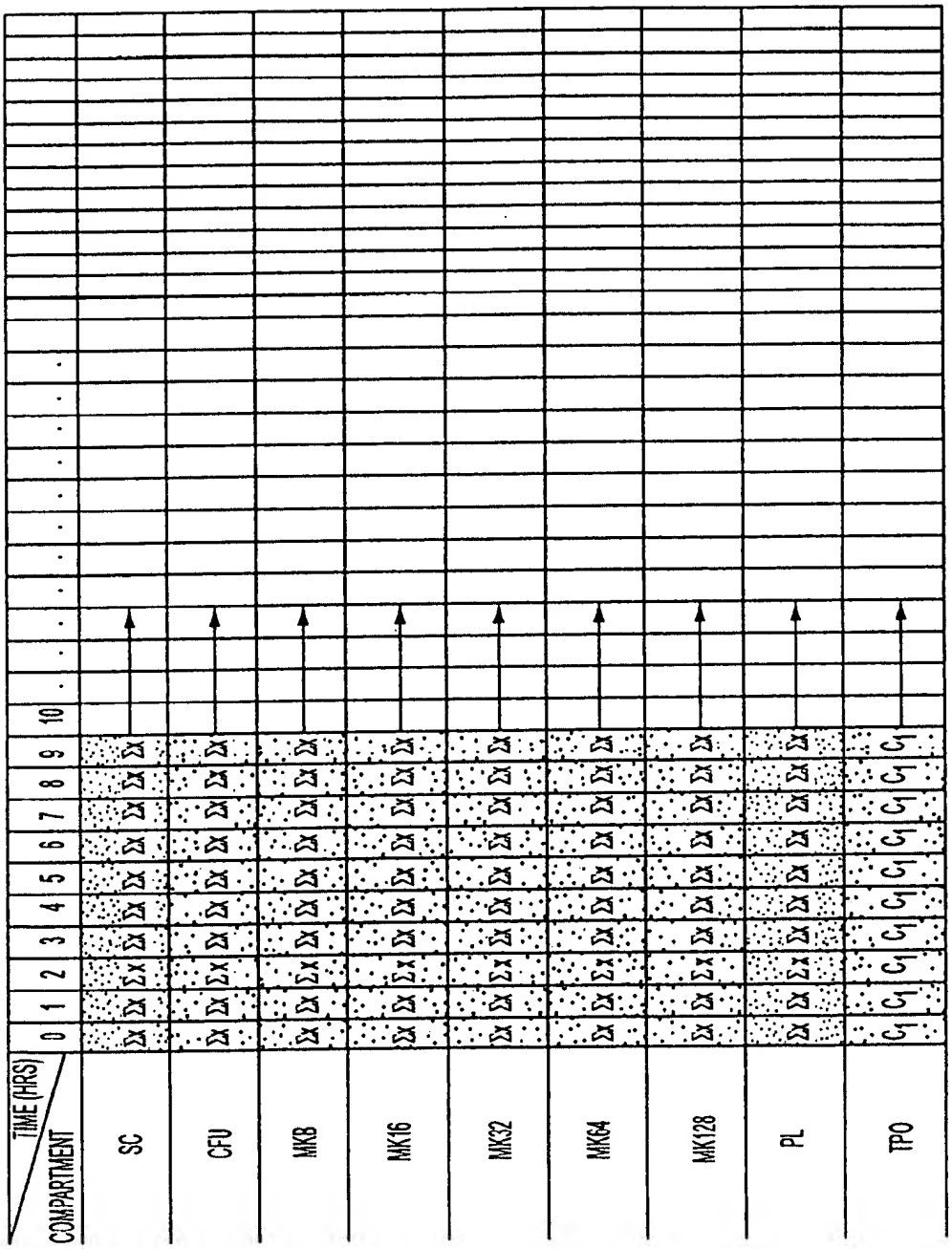
TIME (HRS)
COMPARTMENT
0
1
2
3
4
5
6
7
8
9
10
SC
CFU
MKB
MK16
MK32
MK64
MK128
PL
TPD

FIG. 6

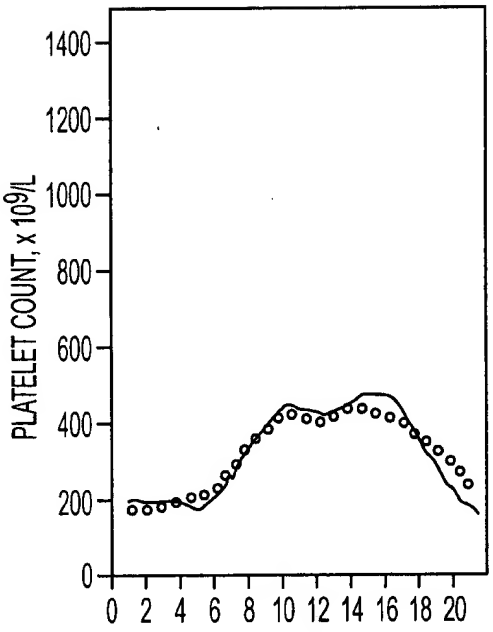
PLATELET COUNT, x 10⁹/L
1400
1200
1000
800
600
400
200
0
0 2 4 6 8 10 12 14 16 18 20

FIG. 7A

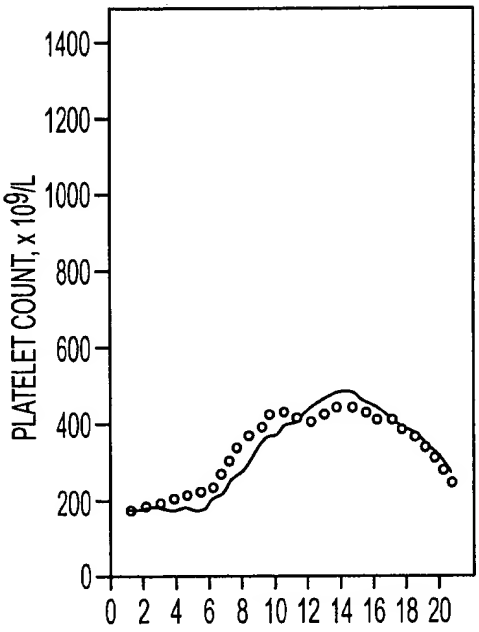
PLATELET COUNT, x 10⁹/L
1400
1200
1000
800
600
400
200
0
0 2 4 6 8 10 12 14 16 18 20

FIG. 7B

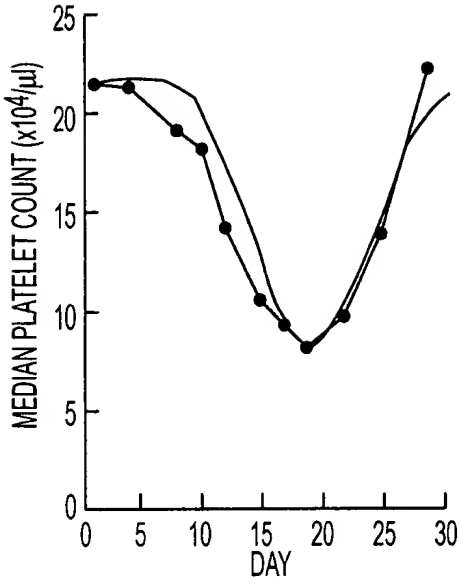
MEDIAN PLATELET COUNT (x10⁴/μl)
0
5
10
15
20
25
0
5
10
15
20
25
30
DAY

FIG. 8A

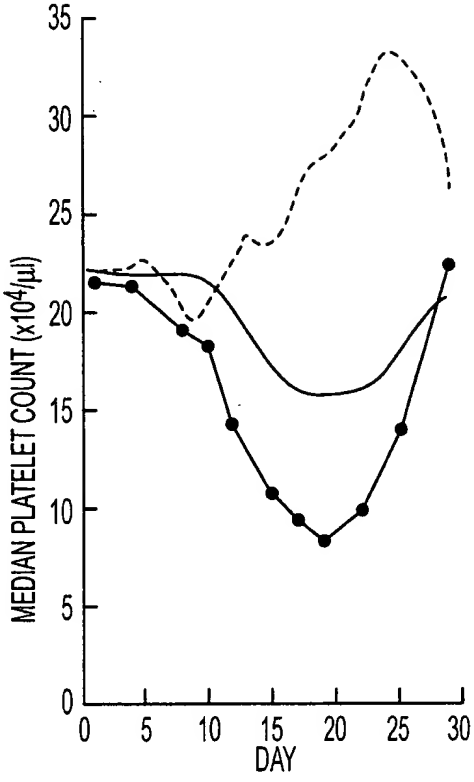
MEDIAN PLATELET COUNT (x10⁴/μl)
0
5
10
15
20
25
30
35
0
5
10
15
20
25
30
DAY

FIG. 8B

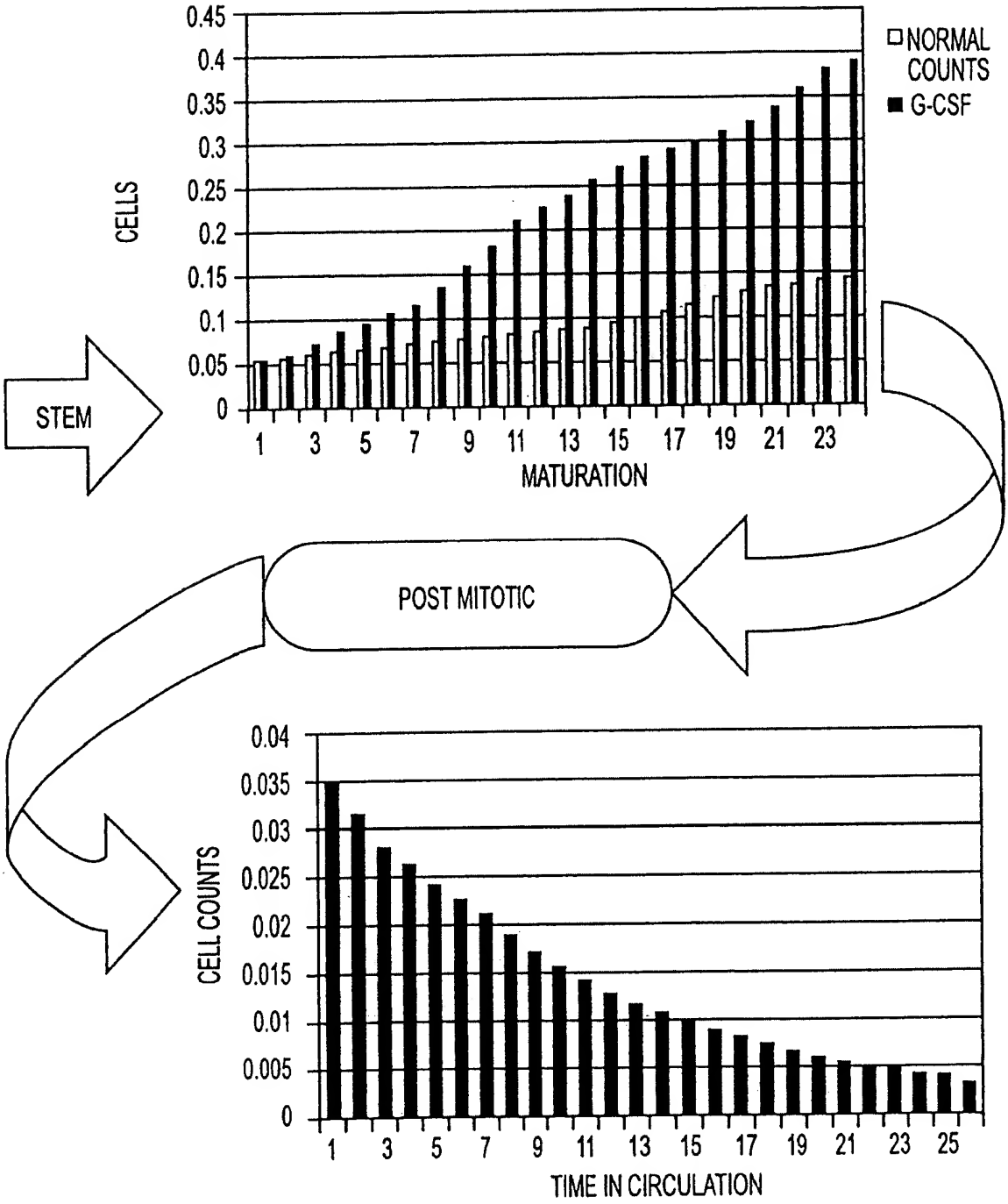
0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
CELLS
NORMAL COUNTS
G-CSF
1 3 5 7 9 11 13 15 17 19 21 23
MATURATION
STEM
POST MITOTIC
0.04
0.035
0.03
0.025
0.02
0.015
0.01
0.005
0
CELL COUNTS
1 3 5 7 9 11 13 15 17 19 21 23 25
TIME IN CIRCULATION

FIG. 9

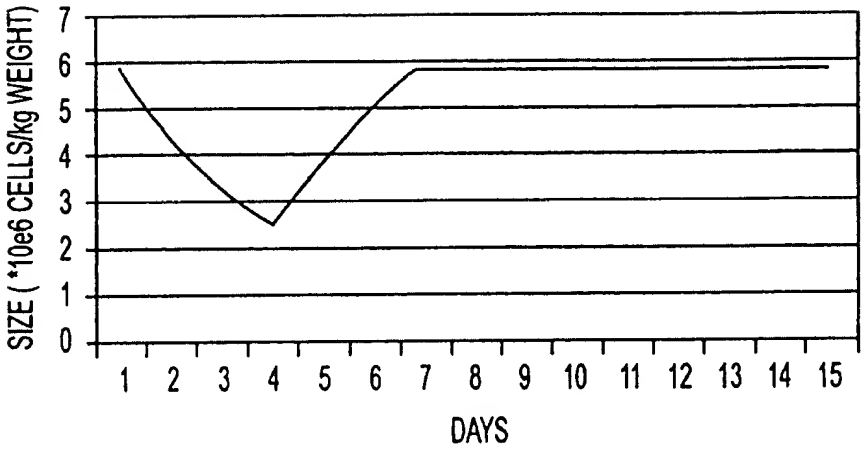
SIZE (*10e6 CELLS/kg WEIGHT)
7
6
5
4
3
2
1
0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
DAYS

FIG. 10

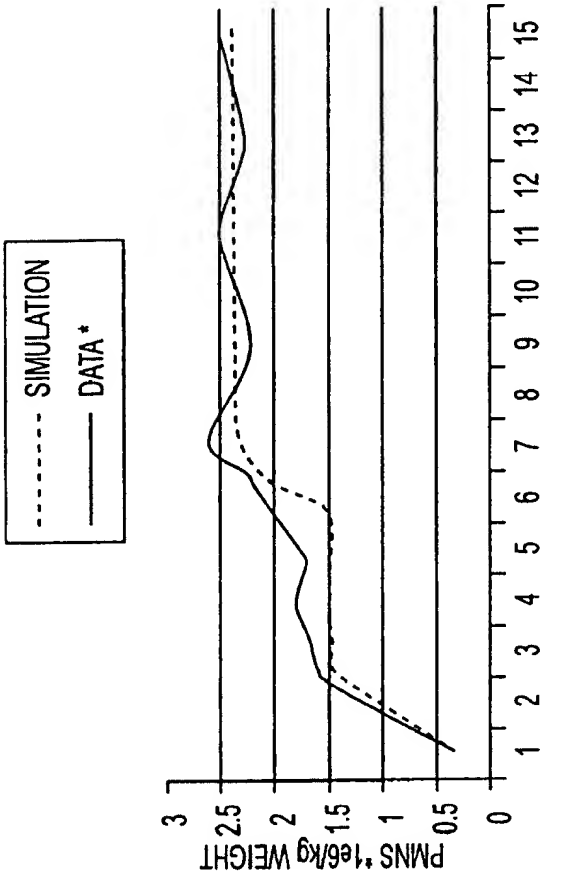

FIG. 11B

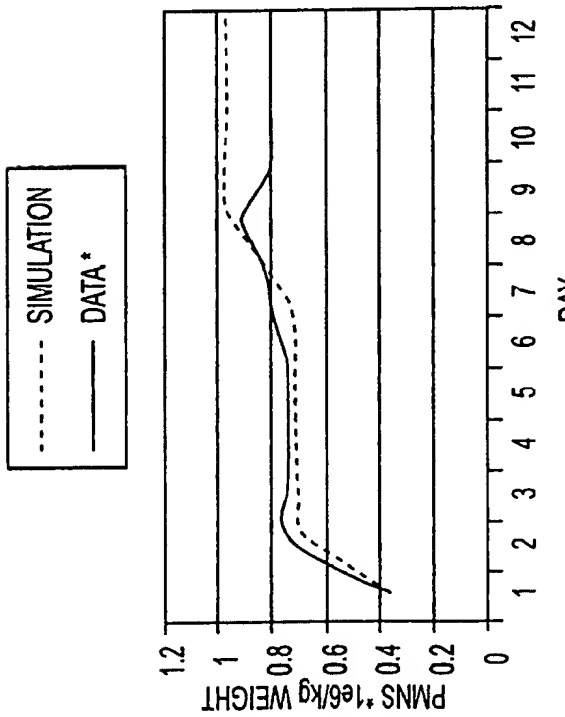

FIG. 11A

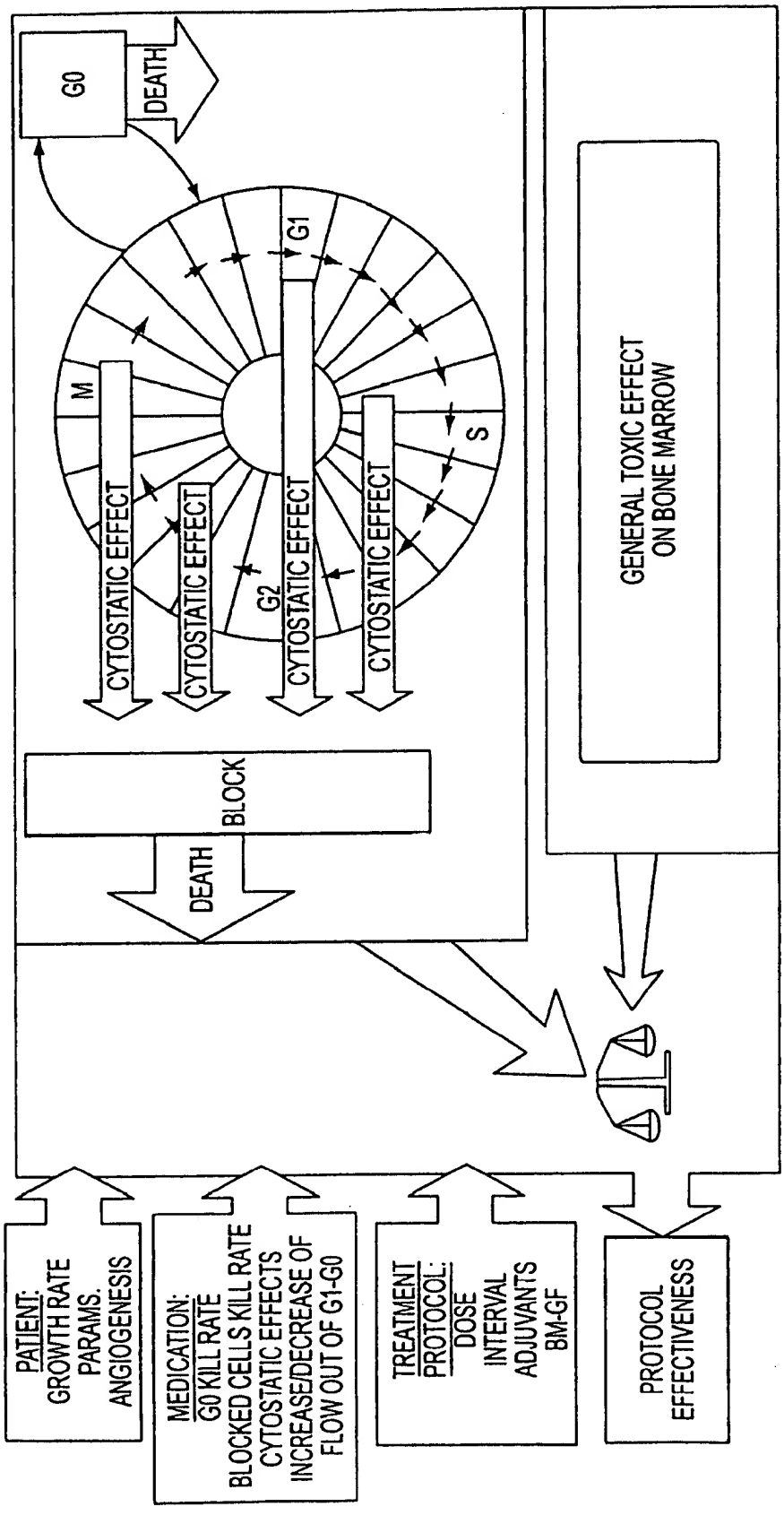
G0
DEATH
G1
M
S
G2
CYTOSTATIC EFFECT
CYTOSTATIC EFFECT
CYTOSTATIC EFFECT
CYTOSTATIC EFFECT
GENERAL TOXIC EFFECT ON BONE MARROW
BLOCK
DEATH
PATIENT:
GROWTH RATE
PARAMS.
ANGIOGENESIS
MEDICATION:
G0 KILL RATE
BLOCKED CELLS S KILL RATE
CYTOSTATIC EFFECTS
INCREASE/DECREASE OF
FLOW OUT OF G1-G0
TREATMENT
PROTOCOL:
DOSE
INTERVAL
ADJUVANTS
BM-GF
PROTOCOL
EFFECTIVENESS

FIG. 12

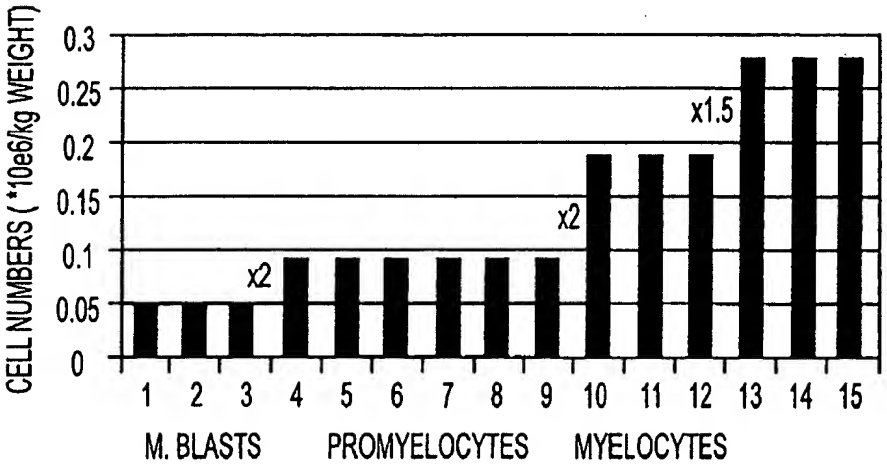
CELL NUMBERS (*10e6/kg WEIGHT)
0.3
0.25
0.2
0.15
0.1
0.05
0
x2
x2
x1.5
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
M. BLASTS
PROMYELOCYTES
MYELOCYTES

FIG. 13

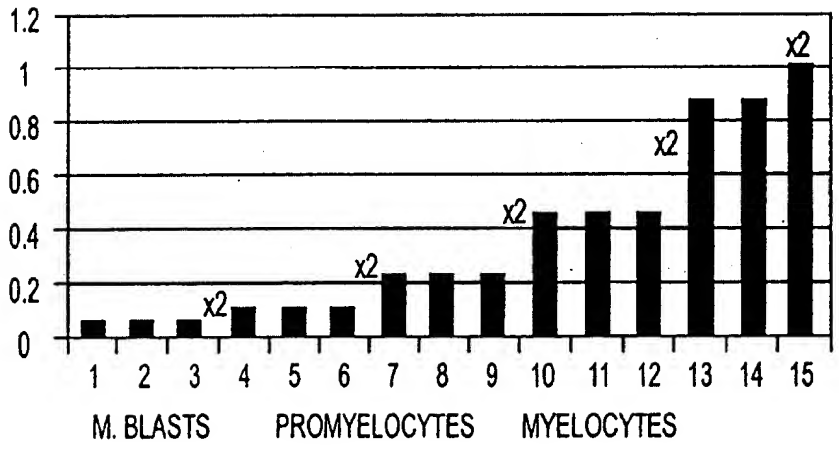
1.2
1
0.8
0.6
0.4
0.2
0
x2
x2
x2
x2
x2
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
M. BLASTS
PROMYELOCYTES
MYELOCYTES

FIG. 14